Remarks

Claims 1 through 41 remain pending in the application.

The Office Action maintains the rejections stated in the Office Action of September 24, 2007 and September 26, 2008. However, those rejections were based on an assertion that a stent "can be placed in the endocardial or peri-adventitial area, which would mean the therapeutic agent will be injected into the myocardium from these areas." The Office Action maintains and reiterates this rejection, despite the clear inadvisability of placing a stent outside the arteries to treat a stenotic lesion inside the artery. The fact that the claims are found unpatentable based on the assumption that one in the art would install a coronary stent outside the coronary artery is a clear sign that the claims are non-obvious, because the reason suggested for doing so is so blatantly dangerous and deadly to the patient and will not lead to any alleviation of the stenosis of the coronary artery treated with a stent placed in the endocardial or peri-adventitial space.

The arguments traversing the rejections stated in the Applicant's prior response are reiterated.

In response, the Examiner asserts that the above arguments are not persuasive and that Stevens discloses the method as claimed. This is a new rejection, not previously raised, that Stevens anticipates the claims.

In support of the rejection of claims 1, 3, 5, 6, 11, 13, 15, 16, 21, 23, 25, 26, 31, 33, 35 and 36 as anticipated by Stevens, the Examiner asserts that Stevens teaches a method of

treating restenosis comprising the steps of implanting a stent with radially protruding needles and injecting therapeutic agent into the surrounding myocardium through the blood vessel wall, citing col. 10, ll. 18-24 of Stevens, and the further assertion that Stevens discloses injecting an anti-restenosis agent into the myocardium, citing col. 2, ll. 38-48.

The Examiner seems to be reporting that Stevens mentions anti-restenosis agents in col. 2, ll. 38-48. However, it is clear that Stevens does not mention anti-restenosis agents. The cited passage is undebatable on this point. For this reason alone, the anticipation rejection of claim 1 fails and should be withdrawn. While Stevens suggests that needles on the outside of the stent in his Figure 15 penetrate the artery wall, those needles are not hollow, and are not connected to any source of injectable therapeutic agent, and certainly cannot inject into the myocardium if they do not even reach the myocardium. Stevens' needles have a coating, as mentioned in the uncited passages leading up to the passage relied on by the Examiner, but this does not imply injection of some injectable agent. For this reason alone, Stevens does not anticipate claim 1, and the anticipation rejection should be withdrawn. Regarding both bases for rejection, it seems that the Examiner is using odd, non-standard definitions of common terms. The Applicant requests that the Examiner disclose the bases for definitions of the claim language that are unique to the Examiner and not shared by artisans. Otherwise, as here, the Applicant cannot adequately address the rejections.

As to claim 3, there is no indication that Stevens injects anything through the needles on his stent. The needles are

merely coated with something which the Examiner misunderstands to be an anti-restenosis agent.

As to claim 5, the rejection ignores limitations of the claim. Claim 5 requires that the agent be injected at a site distal to the stent. This is clearly not possible with the Stevens stent, since his spikes are fixed to the stent.

As to claim 6, the rejection ignores limitations of the claims, which include specific anti-restenosis agents.

As to claim 11, Stevens does not disclose or suggest combining angioplasty with injection of anything, including the specifically recited anti-restenosis agent. The limitations of the dependent claims 13 (peri-adventitial delivery through the vessel wall), 15 (distal injection) 16 (specific anti-restenosis agents) are not disclosed in combination with angioplasty. Thus, each of the anticipation rejections should be withdrawn.

Regarding claim 21, Stevens does not disclose injection of an anti-restenosis agent to treat a coronary blood vessel, or the limitations of the dependent claims. Thus, each of the anticipation rejections should be withdrawn.

Regarding claim 31, Stevens does not disclose injection of an anti-restenosis agent to treat an intraluminal disease of a coronary blood vessel, or the limitations of the dependent claims. Thus, each of the anticipation rejections should be withdrawn.

The Office Action rejects claims 4, 14, 24 and 34 as obvious over Stevens. The obviousness rejections are based on the anticipation rejections of the base claims, which are

traversed above. These claims should be allowed as dependent on allowable base claims.

The Office Action rejects claims 7, 8, 17, 27, 28, 27 and 38 as obvious over Stevens. The obviousness rejections are based on the anticipation rejections of the base claims, which are traversed above. These claims should be allowed as dependent on allowable base claims. Moreover, Stevens' disclosure is fairly clear that the needles attached to the stent are not hollow, and are not attached to any source through which any substance might be injected, so that the stated basis for the rejection is not supported by the disclosure of Stevens.

The Office Action rejects claims 8-10, 18-20, and 38-40 as obvious over Stevens in view of Mixson, Carrier: DNA complexes containing DNA encoding anti-angiogenic peptides and their use in gene therapy, U.S. Patent 6,080,728 (Jun. 27, 2000). The obviousness rejections are based on the anticipation rejections of the base claims, which are traversed above. These claims should be allowed as dependent on allowable base claims. Moreover, as discussed in earlier responses, Mixson does not provide any suggestion to use his compounds for controlling stenosis, or doing so in combination with stent placement. Mixson teaches use of anti-angiogenic proteins to kill tumors. Even considered with the other references, Mixson does not suggest use in the claimed method. This rejection, like the rejection of the parent claims, is not supported by any purported motivation to make the combination. The examiner does not suggest how artisans would suspect that, if injected into the myocardium downstream in the coronary vasculature relative to a stenotic lesion, Mixson's compounds would have any beneficial effect on the stenotic lesion. The more likely

expectation, from the knowledge that Mixson's compounds were useful to suppress tumors, would be some deleterious effect on the function of the heart wall. In light of the deleterious effect that Mixson's compounds have on tumors into which they are injected, Applicant suggests that it would require an explicit suggestion in the art to accomplish the claimed method. In any event, the utter lack of a motivation to make the combination indicates that a prima facie case of obviousness has not been made out, and the claims should be allowed.

As the Applicant has previously pointed out, neither the pathway nor the agents usefully employed through the pathway are obvious in view of the cited references. Altman, et al., Exploring Heart Lymphatics in Local Drug Delivery, 1 Lymphatic Research And Biology 47, (2003) illustrates the advantage of the claimed method, which could not have been understood by review of the cited art. The article illustrates the behavior of compositions described in the earlier filed specification of the current patent application. As described in this peer-reviewed article, microspheres injected in the myocardium tend to migrate through the lymphatic system of the heart upstream relative the coronary artery and collect in peri-adventitial heart tissue around the coronary artery. They do not quickly dissipate away from the site. The size of the particles effects the rate at which they migrate, degrade, and release agents that then migrate into the coronary vessel wall. As discussed in the article, particles of 15000 nm (described as 15 um in the specification) remain localized near the site of injection. These larger particles gradually decay and migrate up the outside of the coronary artery and slowly release agents to the coronary artery wall. This enables long term release of anti-

restenosis agents which otherwise would be quickly washed out of the coronary system with little or no local effect. Thus, the Applicant has discovered a drug delivery pathway that was unappreciated in the art, and has beneficial attributes unappreciated in the art. Accordingly, the claims directed to combining use of those pathways with stent placement would not have been obvious. The claims directed toward use of those pathways with stent placement and particular formulations (claims 7 through 9, 17 through 19, 27 through 29 and 37 through 39, and claims 10, 20, 30 and 40) would not have been obvious, for the additional reason that the cited art does not suggest any particular motivation to use those formulations in combination with stent placement or peri-adventitial delivery.

The Office Action rejects claims 1, 2, 6-8, 11, 12, 16 through 18, 21, 22, 26 through 28, 31, 32 and 36 through 38 as obvious over Nash, U.S. Patent 6,709,427 (March 23, 2004) (filed Aug. 5, 1999) in view of Stegmann, U.S. Pub. 2002/0122792 (filed July 22, 1999). The proposed combination, however, does not meet the limitations of the claims, which require injection of anti-restenosis agents. Accordingly, no prima facie case of obviousness has been made out, and the rejection should be withdrawn.

Claim 41 is rejected as obvious over Stevens in view of Kunz, Therapeutic inhibitor of vascular smooth muscle cells, U.S. Patent 5,981,568 (Nov. 9. 1999), under the assertion that Stevens discloses the step of positioning a catheter into a desired location, and that it would have been obvious to provide instructions just as Kunz provided instructions.

This rejection ignores limitations of the claims. The claims require instructions to position the "means for introducing" in the perivascular space to treat a lesion in an intravascular space, and this combination of limitations is not addressed by the rejection. Claim 41 also requires delivering a dose of the therapeutic agent into the perivascular space near the diseased region in the blood vessel. Neither reference, including Stevens, includes this limitation. Stevens positions his stent and his catheter in the blood vessel, the spikes are limited to extending into the blood vessel wall, and neither device extends into the perivascular space. The proposed combination does not meet the limitations of the claims, and no prima facie case of obviousness has been made out.

Conclusion

This response has addressed all of the Examiner's grounds for rejection. The rejections based on prior art have been traversed. Reconsideration of the rejections and allowance of the claims is requested.

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